II. AMENDMENTS

In the Claims:

1. (Previously presented) A non-single-chain antigen-binding unit comprising:

   (a) a light (L) chain polypeptide comprising a light (L) chain variable region fused in-frame to a first heterodimerization polypeptide;

   (b) a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused in-frame to a second heterodimerization polypeptide;

   wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization polypeptides; and wherein at least one of the heterodimerization polypeptides is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

2. (Previously presented) The non-single-chain antigen-binding unit of claim 1, wherein both of the first and second heterodimerization polypeptides are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

3. (Previously presented) A non-single-chain antigen-binding unit comprising:

   (a) a light (L) chain polypeptide comprising a light (L) chain variable region fused in-frame to a first heterodimerization polypeptide;

   (b) a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused in-frame to a second heterodimerization polypeptide ;

   wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization polypeptides, said first and second heterodimerization polypeptides comprising polypeptides from heterodimeric receptors that mediate heterodimerization of said receptors.

4. (Previously presented) The non-single-chain antigen-binding unit of claim 1 or 3, wherein the first and second heterodimerization polypeptides form a coiled-coil dimer.

5. (Previously presented) The non-single-chain antigen-binding unit of claim 1 or 3, wherein the L and the H chain polypeptides dimerize via non-covalent pairwise affinity of the two heterodimerization polypeptides.

6. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the L chain polypeptide further comprises a flexon that is flanked by the L chain variable region and the first heterodimerization polypeptide.

7. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the H chain polypeptide further comprises a flexon that is flanked by the H chain variable region and the second heterodimerization polypeptide.

8. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein at least one cysteine residue is linked to the first heterodimerization polypeptide, and at least one cysteine residue is linked to the second heterodimerization polypeptide, so that the first and second heterodimerization polypeptides are linked to each other via a disulfide bond.

9. (Original) The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is multivalent.

10. (Original) The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is multispecific.

11. (Original) The non-single-chain antigen-binding unit of claim 10, wherein the antigen-binding unit is bispecific.

12. (Original) The non-single-chain antigen-binding unit of claim 10, wherein the antigen-binding unit is trispecific.

13. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the L chain polypeptide comprises a polypeptide from a human light chain.

14. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the H chain polypeptide comprises a polypeptide from a human heavy chain.

15. (Original) The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is conjugated to a chemically functional moiety.

16. (Original) The non-single-chain antigen-binding unit of claim 15, wherein the moiety is selected from the group consisting of signal peptides, agents that enhance immunologic reactivity, agents that facilitate coupling to a solid support, vaccine carriers, bioresponse modifiers, toxins, detectable labels, paramagnetic labels, and drugs.

17. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the first and second heterodimerization polypeptides are from C-terminal polypeptide of $GABA_B$ receptor 1 and $GABA_B$ receptor 2, respectively.

18. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the first heterodimerization polypeptide comprises a $GABA_B$ receptor 1 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 2 and wherein the second heterodimerization polypeptide comprises a $GABA_B$ receptor 2 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 4, wherein said first and second heterodimerization polypeptides are linked to cysteine residues, so that the first and second heterodimerization polypeptides are linked to each other by a disulfide bond.

19. (Previously presented) The non-single-chain antigen-binding unit of claim 4, wherein the first heterodimerization polypeptide comprises a $GABA_B$ receptor 1 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 4; and wherein the second heterodimerization polypeptide comprises a $GABA_B$ receptor 2 polypeptide of at least

30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 2, wherein said first and second heterodimerization polypeptides are linked to cysteine residues, so that the first and second heterodimerization polypeptides are linked to each other by a disulfide bond.

20. (Currently amended) A single-chain antigen-binding unit comprising a light ~~(L)~~ chain variable region (VL) and a heavy ~~(H)~~ chain variable region (VH) connected by a first and a second heterodimerization polypeptide spanning the distance between the C-terminus of one of the region to the N-terminus of the other region in the configuration of VH—(first heterodimerization sequence)-(second heterodimerization sequence) —VL or VL—(first heterodimerization sequence)-(second heterodimerization sequence) —VH, ~~as shown in Figure 18,~~ wherein the two regions form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization polypeptides; and wherein at least one of the heterodimerization polypeptides is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

21. (Previously presented) The single-chain antigen-binding unit of claim 20, wherein both of the first and second heterodimerization polypeptides are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

22. (Currently amended) A single-chain antigen-binding unit comprising a light ~~(L)~~ chain variable region (VL) and a heavy ~~(H)~~ chain variable region (VH) connected by a first and a second heterodimerization polypeptide spanning the distance between the C-terminus of one of the region to the N-terminus of the other region in the configuration of VH—(first heterodimerization sequence)-(second heterodimerization sequence) —VL or VL—(first heterodimerization sequence)-(second heterodimerization sequence) —VH, ~~as shown in Figure 18~~, wherein the two regions form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization polypeptides, said first and second heterodimerization polypeptides comprising

polypeptides from heterodimeric receptors that mediate heterodimerization of the receptors.

23. (Previously presented) The single-chain antigen-binding unit of claim 20 or 22, wherein the first and second heterodimerization polypeptides form a coiled-coil dimer.

24. (Previously presented) The single-chain antigen-binding unit of claim 20 or 22, wherein the first and second heterodimerization polypeptides dimerize via non-covalent pairwise affinity.

25. (Original) The single-chain antigen-binding unit of claim 23, wherein the antigen-binding unit is conjugated to a chemically functional moiety.

26. (Previously presented) The single-chain antigen-binding unit of claim 23, wherein the L chain variable region comprises a polypeptide from a human light chain.

27. (Previously presented) The single-chain antigen-binding unit of claim 23, wherein the H chain variable region comprises a polypeptide from a human heavy chain.

28. (Previously presented) The single-chain antigen-binding unit of claim 23, wherein the first and second heterodimerization polypeptides are from C-terminal polypeptide of $GABA_B$ receptor 1 and $GABA_B$ receptor 2, respectively.

29. (Previously presented) The single-chain antigen-binding unit of claim 23, wherein the first heterodimerization polypeptide comprises a $GABA_B$ receptor 1 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 2; and wherein the second heterodimerization polypeptide comprises a $GABA_B$ receptor 2 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 4, wherein said first and second heterodimerization polypeptides are linked to cysteine residues, so that the first and second heterodimerization polypeptides are linked to each other by a disulfide bond.

30. (Previously presented) The single-chain antigen-binding unit of claim 23, wherein the first heterodimerization polypeptide comprises a $GABA_B$ receptor 1 polypeptide of at

least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 4; and wherein the second heterodimerization polypeptide comprises a $GABA_B$ receptor 2 polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide of identical length, contained in SEQ ID NO. 2, wherein said first and second heterodimerization polypeptides are linked to cysteine residues, so that the first and second heterodimerization polypeptides are linked to each other by a disulfide bond.

31. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes L chain polypeptide of claim 1.

32. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes the H chain polypeptide of claim 1.

33. (Withdrawn) A recombinant polynucleotide comprising a first coding sequence that encodes the L chain polypeptide of claim 1, and a second coding sequence that encodes the H chain of polypeptide of claim 1.

34. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes the L chain polypeptide of claim 3.

35. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes the H chain polypeptide of claim 3.

36. (Withdrawn) A recombinant polynucleotide comprising a first coding sequence that encodes the L chain polypeptide of claim 3, and a second coding sequence that encodes the H chain of polypeptide of claim 3.

37. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 20.

38. (Withdrawn) A recombinant polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 22.

39. (Withdrawn) A vector comprising the recombinant polynucleotide of any one of claims 31-38.

40. (Withdrawn) The vector of claim 39, wherein the vector is an expression vector.

41. (Withdrawn) The vector of claim 39, wherein the vector is a phage display vector.

42. (Withdrawn) A selectable library of expression vectors encoding a repertoire of antigen binding units, comprising more than one vector of claim 39.

43. (Withdrawn) The selectable library of claim 39, wherein the vector is a phage display vector.

44. (Withdrawn) A host cell comprising the recombinant polynucleotides of any one of claims 31-38.

45. (Withdrawn) The host cell of claim 44, wherein the recombinant polynucleotide encoding the L chain polypeptide and the polynucleotide encoding the H chain polypeptide, are present in a single vector.

46. (Withdrawn) The host cell of claim 44, wherein the recombinant polynucleotide encoding the L chain polypeptide and the polynucleotide encoding the H chain polypeptide, are present in separate vectors.

47. (Withdrawn) The host cell of claim 44, wherein the host cell is a eukaryotic cell.

48. (Withdrawn) The host cell of claim 44, wherein the host cell is a prokaryotic cell.

49. (Withdrawn) A method of producing a non-single-chain antigen-binding unit, comprising:

(a) expressing in a host cell a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused in-frame to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused in-frame to a second heterodimerization sequence; wherein the L

chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures; and optionally

(b) isolating the antigen-binding unit expressed in the host cell.

50. (Withdrawn) A method of claim 49, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

51. (Withdrawn) A method of producing a non-single-chain antigen-binding unit, comprising:

(a) expressing in a host cell a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused in-frame to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused in-frame to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences, said first and second heterodimerization sequences comprising heterodimeric receptor sequences that mediate heterodimerization of the receptors; and optionally

(b) isolating the antigen-binding unit expressed in the host cell.

52. (Withdrawn) The method of claim 49 or 51, wherein the non-single-chain antigen-binding expressed in step (a) is displayed on surface of the host cell.

53. (Withdrawn) The method of claim 49 or 51, wherein the non-single-chain antigen-binding expressed in step (a) is displayed on a phage particle.

54. (Withdrawn) The method of claim 49 or 51, wherein the host cell is a eukaryotic cell.

55. (Withdrawn) The method of claim 49 or 51, wherein the host cell is a prokaryotic cell.

56. (Withdrawn) The method of claim 49 or 51, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

57. (Withdrawn) The method of claim 49 or 51, wherein the L chain and the H chain polypeptides dimerize via non-covalent pairwise affinity.

58. (Withdrawn) The method of claim 56, wherein the L chain polypeptide further comprises a flexon that is flanked by the L chain variable region and the first heterodimerization sequence.

59. (Withdrawn) The method of claim 56, wherein the H chain polypeptide further comprises a flexon sequence that is flanked by the H chain variable region and the second heterodimerization sequence.

60. (Withdrawn) The method of claim 56, wherein both the first and the second heterodimerization sequences are linked to at least one cysteine residue.

61. (Withdrawn) The method of claim 56, wherein the non-single-chain antigen-binding unit is multivalent.

62. (Withdrawn) The method of claim 56, wherein the non-single-chain antigen-binding unit is multispecific.

63. (Withdrawn) The method of claim 62, wherein the non-single-chain antigen-binding unit is bispecific.

64. (Withdrawn) The method of claim 62, wherein the non-single-chain antigen-binding unit is trispecific.

65. (Withdrawn) The method of claim 56, wherein the L chain polypeptide comprises sequences derived from a human light chain.

66. (Withdrawn) The method of claim 56, wherein the H chain polypeptide comprises sequences derived from a human heavy chain.

67. (Withdrawn) A method of producing a non-single-chain antigen-binding unit, comprising:

(a) preparing a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused in-frame to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused in-frame to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures; and

(b) allowing the first and second polypeptides to dimerize via pairwise affinity of the first and second heterodimerization sequences.

68. (Withdrawn) The method of claim 67, wherein step (b) comprises dimerizing the first and the second polypeptides *in vitro*.

69. (Withdrawn) A method of producing a single-chain antigen-binding unit, comprising:

(a) expressing in a host cell a polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 20 or 22; and optionally

(b) isolating the single-chain antigen-binding unit expressed in the host cell.

70. (Withdrawn) The method of claim 69, wherein the polynucleotide is contained in a phage display vector.

71. (Withdrawn) A method of displaying a chimeric heteromultimer comprising at least two polypeptides on a surface of a host cell, the method comprising:

expressing in the host cell

(a) a first recombinant polynucleotide encoding a first polypeptide fused in-frame to a first heterodimerization sequence and a surface presenting sequence;

(b) a second recombinant polynucleotide encoding a second polypeptide fused in-frame to a second heterodimerization sequence;

wherein the first and second polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

72. (Withdrawn) The method of claim 71, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

73. (Withdrawn) The method of claim 71, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

74. (Withdrawn) The method of claim 71, wherein the first and second polynucleotides are expressed by a single phage display vector.

75. (Withdrawn) The method of claim 71, wherein the first and second polynucleotides are expressed by separate phage display vectors.

76. (Withdrawn) The method of claim 71, wherein the host cell is a prokaryotic cell.

77. (Withdrawn) The method of claim 71, wherein the host cell is a eukaryotic cell.

78. (Withdrawn) The method of claim 71, wherein the chimeric heteromultimer is a non-single-chain antigen-binding unit.

79. (Withdrawn) A chimeric heteromultimer displayed on the surface of the host cell according to the method of claim 71.

80. (Withdrawn) A method of identifying a non-single-chain antigen-binding unit that is immunoreactive with a desired antigen, comprising:

(a) preparing a genetically diverse repertoire of antigen-binding units, wherein the repertoire comprises more than one antigen-binding unit of claim 1 or 3;

(b) contacting the repertoire of antigen binding units with the desired antigen;

(c) detecting a specific binding between antigen binding units and the antigen, thereby identifying the antigen-binding unit that is immunoreactive with the desired antigen.

81. (Withdrawn) The method of claim 80, wherein the repertoire of antigen-binding units are prepared by expressing a library of vectors encoding a plurality of the antigen-binding units.

82. (Withdrawn) The method of claim 80, wherein the library of vectors comprises a plurality of phage vectors.

83. (Withdrawn) A method of identifying a single-chain antigen-binding unit that is immunoreactive with a desired antigen, comprising:

(a) preparing a genetically diverse repertoire of single-chain antigen-binding units, wherein the repertoire comprises at least one antigen-binding unit of claim 20 or 22;

(b) contacting the repertoire of antigen-binding units with the desired antigen;

detecting a specific binding between antigen-binding units and the antigen, thereby identifying the single-chain antigen-binding unit that is immunoreactive with the desired antigen.

84. (Withdrawn) The method of claim 83, wherein the repertoire of antigen-binding units are prepared by expressing a library of vectors encoding a plurality of the antigen-binding units.

85. (Withdrawn) The method of claim 83, wherein the library of vectors comprises a plurality of phage vectors.

86. (Withdrawn) A kit comprising a vector of claim 39 in suitable packaging

87. (Previously presented) A non-single-chain antigen-binding unit of claim 1 or 3, wherein said first and second heterodimerization polypeptides comprise heterodimeric receptor polypeptides of growth factor receptors.

88. (Previously presented) A non-single-chain antigen-binding unit of claim 1 or 3, wherein said first and second heterodimerization polypeptides comprise heterodimeric receptor polypeptides of G-protein-coupled receptors.

89. (Previously presented) A non-single-chain antigen-binding unit of claim 1 or 3, wherein said first and second heterodimerization polypeptides comprise heterodimeric receptor polypeptides of neurotransmitters.

90. (Previously presented) A non-single-chain antigen-binding unit of claim 1 or 3, wherein said first and second heterodimerization polypeptides comprise heterodimeric receptor polypeptides of nuclear hormone receptors.

91. (Previously presented) A non-single-chain antigen-binding unit of claim 1 or 3, wherein the antigen-binding unit is a ccFv fragment.

92. (Previously presented) A non-single-chain antigen-binding unit of claim 1, wherein the physiological body temperatures are at about 37^0C.

93. (Previously presented) A non-single-chain antigen-binding unit of claim 1, wherein said first and second heterodimerization polypeptides are essentially incapable of forming homodimers when mixed in equimolar.

94. <u>(New) The non-single-chain antigen-binding unit of claim 1 or 3 whose apparent binding affinity is at least one order of magnitude higher than a single-chain antigen-binding unit (scFv) that is stabilized by a peptide linker.</u>